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Assembly and signaling of IL-17 receptor complex

Složení a signalizace receptorového komplexu pro IL-17

Bachelor's thesis

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Abstract

Interleukin-17 is a proinflammatory cytokine that contributes to the host protection through initiation and amplification of inflammation. Inflammation is a crucial mechanism of immune system which protects host from invading pathogens and toxic agents. However, uncontrolled activation of the immune system may also promote autoimmune chronic diseases. Due to this, understanding how proinflammatory signaling pathways are activated and propagated is important in order to prevent autoimmune and chronic inflammatory disorders. This text will discuss molecular mechanisms of interleukin-17 signal pathway leading to the progression of inflammatory immune responses with focus on activators and inhibitors of proximal interleukin-17 receptor signaling.

Keywords

Interleukin-17, proinflammatory cytokines, signal transduction, receptor signaling complex, autoimmune disorders, inflammation

Abstrakt

Interleukin-17 jakožto prozánětlivý cytokin přispívá k ochraně hostitele vyvoláním a zesílením zánětlivých imunitních odpovědí. Zánět je jedním z klíčových mechanismů imunitního systému sloužící k vypořádání se s patogeny a obraně před vlivem toxických látek. V případě nedostatečné kontroly se však může vyvinout v chronické autoimunitní onemocnění poškozující vlastní tělo. Z tohoto důvodu je studium a pochopení prozánětlivé signalizace důležité pro zamezení rozvoje autoimunity a chronických zánětlivých onemocnění. Tato práce shrnuje dosavadní poznatky o molekulárních mechanismech signalizace interleukinu-17 vedoucí k rozvoji zánětlivých imunitních reakcí a též se zaměřuje na regulaci signalizace řadou aktivátorů a inhibitorů.

Klíčová slova

Interleukin-17, prozánětlivý cytokin, signální transdukce, receptorový signální komplex, autoimunitní onemocnění, zánět

Contents

List of abbreviations

Ab	Antibody
AA	Amino acid
AD/AR	Autosomal dominant/Autosomal recessive
APC	Antigen presenting cell
APECED	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
ARE	Adenine-uridine-rich region
AREBP	ARE-binding protein
ATP	Adenosintriphosphate
BRF	Butyrate response factor
CBAD	C/EBP-activation domain
C/EBP	CCAAT/Enhancer Binding Protein
CIKS	Connection to IκB kinase and Stress-activated protein kinases
CMC(D)	Chronic mucocutaneous candidiasis (disease)
CNS	Central nervous system
CTLA-8	Cytotoxic T lymphocyte associated antigen 8
DC	Dendritic cell
DUB	Deubiquitinase
EAE	Experimental autoimmune encephalomyelitis
ERK	Extracellular signal-regulated kinases
FN	Fibronectin III-like domain
FRET	Fluorescence resonance energy transfer
G-CSF	Granulocyte colony-stimulating factor
HuR	Human antigen R
IκB-ζ	Inhibitor of NF-κB-ζ
ICAM-1	Intracellular adhesion molecule 1
IFN	Interferon
IKK	IκB kinase
IL	Interleukin
JNK	c-Jun NH_2-terminal kinase
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein 1
NAK	NF-κB-activating kinase

NF-κB	Nuclear factor κB
NK	Natural killer cell
NKT	Natural killer T cell
PGE-2	Prostaglandin 2
PLAD	Pre-ligand assembly domain
SAPK	Stress-activated MAP kinase
SEFEX	SEFIR-extension
SEFIR	Similar expression of fibroblast growth factor and IL-17R
TAK1	Transforming growth factor β-activated kinase
TBK1	TANK binding kinase 1
TGF	Transforming growth factor
TILL	TIR-like loop
TIR	Toll/IL-1 receptor
TNF	Tumor necrosis factor
TRAF	Tumor necrosis factor receptor-associated factor
Tregs	Regulatory T cells
TTP	Tristetraprolin
USP25	Ubiquitin-specific protease 25

1. Introduction

Interleukin-17A (IL-17A, commonly referred to as IL-17) is the founding member of the family of proinflammatory cytokines consisting of five additional members IL-17B, IL-17C, IL-17D, IL-17E (also termed IL-25) and IL-17F. IL-17A plays a crucial role in host defense against yeast infection. However, its function and regulation have long remained unclear. Nowadays, it's highly studied cytokine because of its role in autoimmune disorders and inflammatory pathology [1].

The gene encoding IL-17 was discovered in 1993 in a rodent T cells by subtractive hybridization and originally termed the cytotoxic T lymphocyte associated antigen 8 (CTLA-8) [2]. Murine IL-17A is a glycoprotein that has 63% amino acid identity with human IL-17A. Both are primarily secreted as disulfide-linked homodimers, mainly by specialized subset of $CD4^+$ T cells termed Th17 cells [3].

T cells, together with B cells, form an integral part of adaptive immunity and can be broadly divided into three major classes: cytotoxic T cells ($CD8^+$), helper T cells ($CD4^+$) and regulatory T cells (Tregs) also known as suppressor cells. Activity of $CD8^+$ cytotoxic T cells is leading to the destruction of infected or otherwise damaged cells. $CD4^+$ helper cells contribute to the immune responses by cytokine production. Tregs maintain tolerance to self-antigens and prevent autoimmune diseases by suppression or downregulation of effector lymphocytes proliferation.

Effector $CD4^+$ T helper cells have been classified into several subsets according to cytokines they produce or by which they are regulated [4]. Type 1 (Th1) cells produce predominantly interferon (INF)-γ, whereas type 2 (Th2) population produces mainly interleukin (IL)-4, IL-5 and IL-13 [2]. In addition, a special type of helper T cells is mainly producing IL-17A and IL-17F and is therefore termed Th17. Although Th17 cells are the main producers of IL-17A and IL-17F, certain types of innate immune cells are able to produce these cytokines immediately upon infection or injury [5]. These cells include macrophages, NK, NKT and DC [2, 5]. Thus, IL-17 links adaptive and innate immunity via its production by both adaptive and innate cells. Except for IL-17A and IL-17F, Th17 cells also produce other cytokines such as IL-21 and IL-22 [3].

Th1 cells differentiate in the presence of IL-12, whereas Th2 upon the stimulation of IL-4. By contrast, differentiation of Th17 cells is negatively regulated by products of both

Th1 and Th2, especially INF-γ and IL-4, respectively. In the absence of these cytokines and the presence of TGF-β and IL-6 together with IL-23 secreted by antigen presenting cells (APCs), naive T cells differentiate into Th17 cells [4, 6]. In general, IL-23 is primarily required for the expansion, survival and proliferation rather than the development of this lineage [2, 7, 8]. In addition, both Th1 and Th2 cells respond poorly to the presence of IL-23.

IL-17 production by Th17 cells provide host with the defense against opportunistic fungal and bacterial infections at epithelial surfaces [9], especially *Candida albicans*. In healthy individuals *Candida albicans* acts as a commensal organism, but may cause mucosal infections during host immunodeficiency. In accord, human patients unable to signal via IL-17 suffer from chronic mucocutaneous candidiasis (CMC) or oropharyngeal candidiasis [10-12]. CMC manifests itself by chronic infections of skin, nails and mucosal surfaces [10].

Although IL-17 acts as a key factor during immune responses contributing to host defense, it was also linked to the development of autoimmune inflammatory diseases such as psoriasis, rheumatoid arthritis and asthma [13]. Due to the role of IL-17 in autoimmune disorders, several therapeutical agents, especially a variety of monoclonal antibodies targeting IL-17/IL-23 axis have been developed and are either used in clinic or tested in pre-clinical trials [14-16]. These antibodies are divided into classes according to target molecule: first class targets IL-23/IL-12 and includes for example ustekinumab. Ustekinumab binds into p40 subunit of IL-23/IL-12, neutralizing their activity [14, 17]. The second class comprises of antibodies blocking IL-17 signaling by targeting either IL-17A ligand (secukinumab or ixekizumab) [18-20] or its receptor IL-17RA (brodalumab) [21, 22].

Majority of these monoclonal antibodies are humanized IgG1 and are used for the treatment of autoimmune diseases, especially for the treatment of moderate-to-severe plaque psoriasis [14, 16]. Therefore, further research in this area has the potential for finding new ways to fight several autoimmune disorders.

2. Interleukin (IL)-17A and its family

Cytokines from IL-17 family, comprising of IL-17A to IL-17F, share considerable degree of similarity, but have no amino acid sequence similarity with any other groups of cytokines. The most conserved region is in the receptor binding portion at the C-terminus. IL-17A and IL-17F share the highest amino acid sequence identity (50%) within the family. By contrast, IL-17E together with IL-17B and IL-17C are the most distinct from IL-17A as they have longer N-terminal extension [23] and their different biological activities suggests that they may form another subclass of the family [3].

IL-17 family ligands are recognized by family of IL-17 receptors (IL-17R). Again, the structure of IL-17 receptors differs from all other receptor families. IL-17R family comprises of 5 members: IL-17RA which is the founding member of the family, IL-17RB, IL-17RC, IL-17RD and IL-17RE. IL-17RA can oligomerize with a majority of other family members and thus may act as a shared receptor subunit for several members of IL-17 ligand family (Figure 1.) [24]. However, not all receptors such as IL-17RD have been already matched to ligands and their cytokines still remain unknown. Following text is dedicated to biological activity and signal transduction of individual members of IL-17 family, especially IL-17A and IL-17F. These two cytokines are most studied members of IL-17 family, since they are strongly involved in inflammatory pathologies and development of autoimmune diseases. However, many principles of their signal pathway will likely be common for other family members.

2.1. IL-17A and IL-17F biology

Genes encoding closely related IL-17A and IL-17F are located on the same chromosome in human genome. Both IL-17A and IL-17F are expressed mainly by activated Th17 cells and secreted as homodimers, although they can also form IL-17A/F heterodimer [25-27]. Both homodimers and heterodimers bind the same receptor composed of IL-17RA and IL-17RC subunits. IL-17RA subunit is expressed widely on various tissues and cell types, whereas IL-17RC is primarily expressed by cells of non-hematopoietic origin, especially epithelial cells [1]. Although the affinity of IL-17F with receptor complex is lower than IL-17A, its signaling results in similar downstream activities [23].

Both IL-17A and IL-17F provide host with the defense against extracellular invading pathogens. Binding of IL-17A or IL-17F to its receptor on epithelial, endothelial and

fibroblastic cells leads to production and secretion of proinflammatory cytokines, which activate immune system and promote recruitment of neutrophils and macrophages [1, 12, 28]. These cytokines include tumor necrosis factor α (TNF-α), IL-1β, granulopoiesis factors such as granulocyte colony-stimulating factor (G-CSF), prostaglandin 2 (PGE2), neutrophil-activating factors (chemokines such as CXCL1 and CXCL2) and acute phase proteins such as IL-6 and IL-8. IL-17 stimulation also induces expression of the intracellular adhesion molecule-1 (ICAM-1) on surface of fibroblasts. In addition, IL-17 stimulation leads to the production of metaloproteases and antimicrobial peptides such as defensins and mucins [1, 12, 23]. Due to this, IL-17 production bridges adaptive and innate immunity during immune responses.

Apart from host defense, IL-17A acts as a key molecule that regulates inflammatory and autoimmune diseases, especially psoriasis and rheumatoid arthritis. IL-17F is also involved in asthma [26].

Psoriasis is widespread chronic autoimmune skin disease affecting 2 to 3 % of human population. It's caused by activity of a variety of proinflammatory cytokines and is substantially influenced by genetic predispositions [29]. Characteristic sign of psoriasis is activation and hyperproliferation of keratinocytes, thus causing distinguishable plaques. Some patients also develop psoriatic arthritis characteristic of joint inflammation. IL-17 has been linked to the development of psoriasis via stimulation of keratinocytes to chemokine expression, leading to the recruitment of other immune cells and thus induction and progression of inflammation. Apart from IL-17A and IL-17F, the other member of IL-17 family IL-17C is able to stimulate keratinocytes and thus cause psoriatic plaques. However, its role is still poorly understood and out of these three cytokines IL-17A was found to be the most active one [30].

Rheumatoid arthritis is chronic autoimmune disease primarily affecting joints. It's characteristic of swollen and painful joints, in later stages leading to destruction of articular cartilage. Both genetic and environmental factors are involved in the development of disease. IL-17A contributes to the disease development by its impact on synoviocytes and osteoblasts, whose stimulation leads to production of other proinflammatory cytokines, such as IL-6, which causes synovitis and joints destruction [31, 32].

Nowadays, treatment of both these autoimmune diseases is based on using various biological agents, especially a variety of suppressors and monoclonal antibodies that targets proinflammatory cytokines responsible for disease progression.

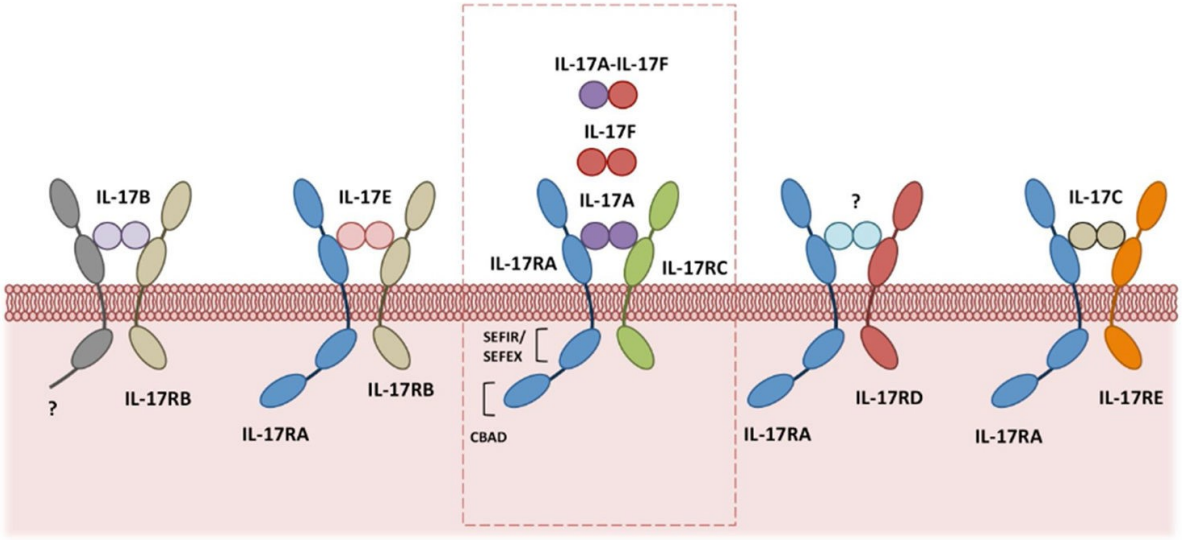

Figure 1. IL-17 family members: *IL-17 ligand family consists of 6 members, IL-17A to IL-17F, while IL-17 receptor family comprises of 5 members IL-17RA to IL-17RE. IL-17RA oligomerizes with majority of other family members, thus forming heteromeric receptors for IL-17 ligands. Each receptor contains cytoplasmic SEFIR domain, only IL-17RA subunit also consists of CBAD domain that differentiates this subunit from other members. Adapted from [33].*

3. Molecular mechanisms of IL-17A/F signal pathway

The mechanism of IL-17A/F signal transduction is still not fully studied and further research is needed for its complete understanding. This bachelor's thesis focuses on the description and characterization of the process of IL-17 signal pathway at molecular level. Complete understanding of IL-17 signal transduction might reveal new targets for treatment of autoimmune diseases and regulation of inflammation development and provide understanding how certain autoimmune diseases, such as psoriasis, are propagated.

3.1. Structural features of IL-17A/F binding to its receptor IL-17RA/RC

IL-17A with its unique structural features forms a novel cytokine family. The major structural distinction from other cytokines is the assembly of unique cysteine knot fold. Cysteine knot fold is a protein motif composed of 2 pairs of β-strands linked together with three disulfide-bonds formed by pairs of cysteine residues [23]. IL-17A contains five cysteine residues, but only four of them are implicated in cysteine knot fold assembly, thus forming different linkage of 2 β-strands. In comparison, cysteine knot fold of other cytokine groups in formed with contribution of all 6 cysteine residues which mediate common knot assembly [27].

IL-17A and IL-17F are the most identical members of IL-17 cytokine family. Although they are structurally and sequentially similar, IL-17F contains one more cys-cys pair that functions as an extra disulfide bond [25]. Both IL-17A/F are secreted as disulfide-linked homodimers or as IL-17A/F heterodimers. Either homodimers and heterodimers are biologically active and can trigger the activation of signaling pathways upon receptor binding. Their receptor is compounded of IL-17RA/IL-17C subunits, thus forming heteromeric complex containing 2 ligand binding sites for IL-17 dimers. Both IL-17RA and IL-17RC subunit are needed for signal transduction [34].

IL-17RA is a transmembrane receptor that forms either homodimeric (two IL-17RA subunits) or heterodimeric complex (with IL-17RC). However, only IL-17RA/RC heteromeric receptor complex is able to signal upon IL-17A/F stimulation [35]. In general, association of receptor subunits is crucial for triggering of signal pathways. Association of some receptor subunits was originally considered to be enabled by ligand binding. However, some subunits

such as IL-17RA was found to preassemble and multimerize in plasma membrane even in the absence of ligands, suggesting their ligand-independent assembly [36, 37]. Nevertheless, IL-17RA forms an inactive structure until ligand binding and only ligand binding mediates its essential conformational changes leading to association of second IL-17RC subunit and enabling initiation of signal pathway [35, 37].

Extracellular domain of both IL-17RA and IL-17RC contains two fibronectin III-like (FN) domains termed FN1 (amino acid residues 69-183) and FN2 (residues 205-282) [36, 38]. These domains are bridged by non-structured 18-amino acid long FN-linker (residues 184-204), which stabilizes the interaction between both domains [24, 36]. In IL-17RA, FN2 domain was identified to drive ligand-independent multimerization and thus considered to constitute a "pre-ligand assembly domain" (PLAD), while FN1 was not able to self-associate [36]. In addition, a ligand binding site was discovered to be located completely in FN2 domain, partially encoded by FN2-linker. Although FN1 is not able to bind ligand alone, it increases the affinity of interaction between IL-17 ligand and receptor as well as between receptor subunits. Moreover, the absence of FN1 appreciably reduces IL-17-dependent signaling. Thus, both FN1 and FN2 together with FN-linker of IL-17RA are required for interaction between IL-17 ligand and receptor leading to induction of signal pathway [36].

3.2. Intracellular domains of IL-17RA/RC are essential for signal transmission

In cytoplasmic domain of IL-17R family was identified a conserved cytoplasmic motif called "similar expression of fibroblast growth factor and IL-17R" (SEFIR) that can be found within all IL-17R family members. This motif has a homology to Toll/IL-1 receptor (TIR)-like domain found in IL-1 and Toll-like receptor family members [24, 39, 40]. However, SEFIR domain in IL-17R lacks some motifs typically found in TIR-domains such as BB-loop and propagation of signaling via IL-17RA and IL-17RC does not require specific TIR adaptors such as MyD88 and TRIF [39].

Instead, SEFIR domain in IL-17RA and IL-17RC interacts with SEFIR motif of another component of IL-17 signal pathway, nuclear factor NF-κB activator 1 (Act1), also known as "connection to IκB kinase and stress-activated kinase" (CIKS) or TRAF3-interacting protein 2 (TRAF3IP2) which acts as a key protein promoting downstream signal transduction. Deletion in SEFIR motif either in IL-17RA or IL-17RC disables Act1 binding and completely prevents signaling [34, 41].

In addition to SEFIR domain, another motif was identified in cytoplasmic domain of IL-17RA. This motif was termed "TIR-like loop" (TILL) as it has specific homology with TIR-like BB-loop [39]. TILL motif is partially overlapping with the SEFIR domain and the deletion of either SEFIR or TILL motifs leads to the inability to recruit Act1 and to respond to IL-17. Thus, both SEFIR and TILL domains appeared as a crucial for IL-17-mediated signaling and activation of NF-κB [39].

Apart from SEFIR/TILL domain, another motif was found within the cytoplasmic tail of IL-17RA. It extends about 100 amino acid residues beyond SEFIR/TILL motifs and was thus termed SEFEX (SEFIR-extension). The deletion in this region suggests that all mentioned motifs are essential for IL-17-mediated signal pathway. According to these observations, it's possible that both SEFIR and SEFEX domains form one compact region than two separated subdomains [42].

In addition to SEFIR/SEFEX region, another structural domain was identified in IL-17R family with no homology to other molecules [39]. It's located in C-terminal ending of IL-17RA cytoplasmic tail, separately from other cytoplasmic subdomains. This motif contributes to the activation of transcription factor CCAAT/enhancer binding protein (C/EBP)-β and thus was termed CBAD domain (C/EBPβ-activation domain) [43]. Activation of both C/EBPβ and C/EBPδ is dependent on SEFIR/TILL domain activity. However, C/EBPβ activation requires additional signal from CBAD motif [39]. In accord, deletion of distant region of IL-17RA results in the activation of C/EBPδ, but not C/EBPβ. Later studies indicated that phosphorylation of C/EBPβ leads to negative signaling events that influence further downstream activities and target genes expression [43]. In summary, cytoplasmic domain of IL-17RA consists of several structurally and functionally important domains that are implicated in IL-17-mediated signaling and are crucial for both positive and negative regulation of this signaling pathway.

3.3. IL-17A/F-mediated signaling

As mentioned above, the major biological activity of IL-17A/IL-17F resides in inducing gene expression of numerous proinflammatory chemokines, cytokines and antibacterial products. This is achieved either by activation of several signaling pathways such as NF-κB (nuclear factor κB), MAPKs (mitogen-activated protein kinases) and C/EBPs or by stabilization of certain mRNA transcripts [33, 44]. Apart from the ability of IL-17A to stimulate other cells for cytokine production, another important aspect of IL-17A function is

its cooperation with other inflammatory cytokines or stimuli. Especially, IL-17A synergizes with TNFα or IL-1, leading to amplification of their biological activities [33, 45].

Following section will describe in detail signal transduction of IL-17A/F and activation of downstream signaling pathways, especially NF-κB, MAPKs and C/EBPs (summarized in Figure 2.).

3.3.1. Activation of transcriptional factors via several signal pathways

NF-κB pathway

Binding of IL-17A, IL-17F homodimers as well as IL-17A/IL-17F heterodimer to its receptor leads to the recruitment of Act1, which results in activation of NF-κB and MAPKs pathways. Act1 contains SEFIR domain in its C-terminus that interacts directly with SEFIR domains of IL-17RA and IL-17RC via homotypic interaction [46, 47]. Although Act1 was proposed to function as nondegradative E3 ubiquitin ligase, its main function is to recruit other E3 ubiquitin ligases, especially TRAF6 [48]. Ubiquitination is a post-translational modification involved in many signaling pathways. This modification requires activity of three enzymes E1, E2 and E3. E1 is an ubiquitin-activating enzyme that binds small protein ubiquitin which contains 76 conserved amino acids. E1 mediates ATP-dependent ubiquitin activation through forming a high-energy thioester bond between C-terminus of ubiquitin and active cysteine of E1. E2, an ubiquitin-conjugating enzyme accepts activated ubiquitins from E1 and E3 enzyme represents ubiquitin ligase that binds E2 enzyme as well as substrate determined for ubiquitination [49, 50]. The process of ubiquitination is based on E3-mediated attachment of activated ubiquitin protein to specific lysine or first methionine (M1) of target substrate and subsequently adding further ubiquitins to the lysine on N-terminus of the previous ubiquitin, which leads to the formation of polyubiquitin chains [49]. Each ubiquitin contains seven lysine residues (K6, K11, K27, K29, K33, K48, K63) and all can be used for formation of different polyubiquitin chains. These different types of polyubiquitin chains have different spatial conformation that can be recognized by different proteins leading to different signaling outcomes [50]. For example, Lys-48-linked (K48) ubiquitination leads to the degradation of target proteins in proteasome, whereas Lys-63-linked (K63) or Met1-linked (M1) ubiquitination promotes nonproteolytic functions such as protein-protein interactions and cell signaling. Both K48 and K63 polyubiquitin chains are essential in regulation of IL-17A/F signal transduction [49, 50].

Nowadays, three families of E3 ubiquitin ligases are known and include HECT (homology to E6AP C-terminus), RING (really interesting new gene) and U-box family [50]. Act1 makes K63 ubiquitination and belongs to the last family of ubiquitin ligases as it contains a region with homology to U3-box, located between 273-338 residues and with E3 ligase activity. Its activity resides in promoting of elongation of poly-ubiquitin chains [51]. Deletion of this region of Act1 prevents its ligase activity and decreases IL-17 signaling. However, the main function of Act1 is to recruit RING E3 ubiquitin ligases from TRAF family, especially TRAF6, which mediates nondegradative K63 poly-ubiquitination [48].

TRAF6 binds to Act1 via its N-terminal part, known as TRAF binding domain [52, 53]. TRAF6 cooperates with dimeric E2 enzyme complex consisting of Ubc13/Uev1A to enable its ligase activity [54, 55]. K63 ubiquitination mediated by TRAF6 is vital for recruitment of several signaling complexes. Transforming growth factor β-activated kinase 1 (TAK1) is recruited to K63 linkages via ubiquitin binding proteins TAB2 and its homolog TAB3, which recognizes ubiquitin linkages via zinc finger motif (ZnF). Mutations in this motif disrupt both binding to polyubiquitin chains and activation of TAK1 [54, 56]. TAK1 is crucial for activation of MAPK pathways and also promotes NF-κB signaling pathway [54].

Another signaling complex recruited to K63 polyubiquitin linkages is IκB kinase (IKK), an enzyme complex consisting of 3 kinase subunits IKKα, IKKβ and NEMO (also known as IKKγ) [56, 57]. IKKα and IKKβ act as catalytic subunits, whereas NEMO binds polyubiquitin chains and serves as a regulatory member of this complex [52]. The role of IKK is to phosphorylate an inhibitor of κB (IκB). In unstimulated cells, IκB forms a complex with NF-κB transcriptional factor, thus preventing NF-κB activation and transport to nucleus [52]. NF-κB is a heterodimeric molecule consisting of 2 subunits p50 and p65 [58]. Upon IL-17 stimulation, TAK1 activates IKK complex via phosphorylation of its IKKβ subunit at two serine residues (S177 and S181) [54, 56]. Activated IKK complex is then able to phosphorylate IκB in IκB/NF-κB complex. This phosphorylation takes place at two serine residues (S32 and S36) and is subsequently recognized by degradative K48 ubiquitin ligase complex consisting of Skp1, Cul1, Roc1/Rbx1 and βTrCP1/2 [56]. This leads to K48-ubiquitination of IκB and its degradation which releases NF-κB and enables its nuclear translocation [33, 55] and NF-κB-dependent transcription of proinflammatory cytokines and chemokines, such as IL-6, IL-8 or CCL2 mRNAs [58].

MAP kinase pathway

Another pathway activated by IL-17A/F stimulation is mitogen-activated protein kinases (MAP kinases, MAPKs) pathway. MAPKs-mediated phosphorylation regulates a wide variety of physiological functions, such as programmed cell death, metabolism and control of cell cycle. However, MAPKs in IL-17 signaling contribute primarily to the regulation of gene expression and their major target substrates are several transcriptional factors [59].

In mammals, three subclasses of MAP kinases were described: ERKs, JNKs and p38 kinases. The activity of MAPKs is mediated by dual phosphorylation of their activation loop motif (T-loop). This phosphorylation is mediated by activity of special phosphorelay system, consisting of three classes of protein kinases, mutually phosphorylating each other. MAPKs, which are able to phosphorylate several substrates, serve as a substrates for MKKs (MAPK kinases). Moreover, MKKs are phosphorylated and thus activated by third class of this system, MKKKs (MAPK kinase kinases). All these classes are, hierarchically, required for final activation of MAPKs and thus regulation of signal transduction [59, 60]. For example, JNKs and p38 kinases are activated by phosphorylation mediated by several MAPKKK, especially MKK4 (SEK1) and MKK7 for JNKs and MKK6 for p38 [58, 60]. Although a majority of MAPKs is activated and regulated by this three-kinase phosphorelay system, in IL-17-induced signaling JNKs and p38 were found to be activated as well by non-MAP kinase molecule TAK1. TAK1 also phosphorylates mentioned MKK6 resulting in JNK-p38 kinase pathway [54]. In general, TAK1 is involved in both activation of NF-κB and MAP kinase pathways, thus connecting these two pathways together and leading to production of a variety of proinflammatory cytokines.

Extracellular signal-regulated kinases (ERKs) has two members, ERK1 and ERK2. They are involved in controlling of cell cycle and activated by several stimuli from cytokines, growth factors and as well from carcinogens and virus infections.

The c-Jun NH_2-terminal kinases (JNKs) family has three members, JNK1-3, that are known as stress-activated MAP kinases (SAPKs). They were termed according to their biological activity, as they are able to bind and thus phosphorylate c-Jun DNA-binding protein [59]. The major biological activity of JNKs is to regulate AP-1 transcriptional factor, which is activated by growth factors, cytokines and also stressed cells [60].

The last, third class represents p38 kinases. This class consists of four kinases p38α-δ, while p38α is the most well described. p38 kinases are activated by inflammatory cytokines and also act as key adaptors in mediating inflammatory immune responses. As other groups of

MAPKs they are able to initiate expression of proinflammatory genes [58, 59]. Moreover, they regulate the stabilization of several inflammatory mRNA transcripts, for example IL-6 and IL-8 mRNAs are highly unstable and p38 was found to be a significant mediator in process of their stabilization [58, 61, 62].

C/EBP pathway

C/EBPs belong to family of transcriptional factors consisting of 6 members: C/EBPα to C/EBPζ and all these members share around 90% sequence identity in C-terminal motif. They were termed after their ability to bind DNA, especially the CCAAT box motif, which could be found in promotors of various genes. This interaction is arranged by their conserved leucine zipper domain located within C-terminus, which contains a high concentration of DNA-binding regions [63]. Due to this, C/EBPs are involved in several physiological processes, including cell differentiation, regulation of metabolism and in case of IL-17A/F they have also effect on initiating inflammatory responses [63]. In addition, expression of some C/EBP family members is influenced by inflammatory agents, particularly a wide variety of cytokines, including IL-17A. Specifically, C/EBPβ and C/EBPδ members are considered to be a main targets of synergistic function of IL-17A/F and TNFα as they together regulate expression of IL-6. As already mentioned, ability of IL-17A to synergize with other proinflammatory stimuli and cytokines is one of its most important functions, contributing to the development of inflammation. This pathway is one of the examples in which the cooperation between IL-17A and TNFα has a special importance [64].

Upon IL-17A/F stimulation, C/EBPβ is phosphorylated at two threonines within its regulatory domain. This phosphorylation is mediated by two mediators: while ERK mediates phosphorylation on T188, glycogen synthase kinase-3β (GSK-3β) phosphorylates C/EBPβ on T179 and this phosphorylation requires previous T188 phosphorylation [43]. This dual phosphorylation causes conformational changes, which facilitate its DNA-binding activity [65]. Phosphorylation of T188 is mediated by SEFIR/TILL domain of IL-17RA/RC, whereas CBAD inhibitory domain is necessary for T179 phosphorylation, thus promoting a negative signal, which down-regulates expression of IL-17A/F target genes [65]. However, deficiency of C/EBPβ and C/EBPδ has no impact to this process [63]. This observation suggests that their function may be compensated by another mediator(s). In summary, IL-17A/F-mediated regulation of inflammatory responses is a functional co-operation between several transcriptional factors and their pathways, including NF-κB, MAPKs and C/EBPs.

Unfortunately, the role of C/EBP pathway in IL-17 signaling is still poorly described and further researches are necessary for its full understanding [63].

3.3.2. IL-17A-mediated stabilization of mRNA transcripts

Apart from induction of proinflammatory gene expression *de novo*, IL-17A/F enhances cytokine gene production by post-transcriptional mRNA stabilization, thus contributing to host defense against pathogens via induction of proinflammatory responses [66, 67]. Each mRNA transcript is predestinated to degradation and its lifetime period is usually very short. The half-life of different mRNA varies according to distinct functions and types of mRNAs. However, the mRNA instability is crucial for possible regulation of protein expression in cells [66]. During inflammation processes the half-life of certain transcripts, e.g. those encoding cytokines, has to be prolonged in order to enhance their production and IL-17A/F stimulation was shown to promote this process. IL-17A stabilizes transcripts of various proinflammatory products, especially chemokines such as CXCL1 (also known as keratinocyte chemoattractant (KC)) which recruits neutrophils to the site of inflammation [67, 68]. Although IL-17A is able to stabilize a variety of mRNA transcripts alone, it is only a moderate stimulator of gene transcription [66]. As mentioned earlier, IL-17A is able to synergize with other inflammatory stimuli and cytokines, such as TNFα by promoting mRNA stabilization. Moreover, IL-17A treatment prolongs a half-life of TNFα-induced CXCL1 mRNA [45, 66] which promotes accumulation of relevant mRNA transcripts.

The probable reason of instability of cytokine, chemokine and other gene mRNAs is presence of adenine-uridine-rich regions (AREs) within 3' untranslated regions of mRNAs [69]. These regions could be recognized by a variety of RNA binding proteins (AREBPs) [61], which mediate mRNAs degradation by several mechanisms including deadenylation, decapping and exonucleolytic degradation [67, 68]. From those, 3' to 5' exonucleolytic degradation is considered to be the major reason for the mRNAs decay [61]. The examples of RNA binding proteins are AUF1 protein, Tristetraprolin (TTP), butyrate response factors (BRF1 and BRF2) and K-homology splicing regulatory protein (KSRP) [67, 68]. In addition, at least two supplemental regulatory mRNA-binding proteins were found to be involved in IL-17A/F-mediated mRNA stabilization, a destabilizing factor SF2/ASF and Human antigen R (HuR). While HuR protein requires IL-17A/F stimulus to mRNA-binding, SF2/ASF binds and destabilizes mRNA in unstimulated cells and IL-17A/F stimulation, contrarily, attenuates the interaction [67].

IL-17A/F enhanced mRNA transcripts stabilization requires Act1, TRAF2 and TRAF5, but not E3 ubiquitin ligase TRAF6, together forming a new signaling complex [70]. These observations suggest that different TRAFs determine and divide downstream functional endpoints [67]. Upon IL-17A/F stimulation, Act1 forms a complex with either TRAF2 or TRAF5 and is able to recruit SF2/ASF destabilizing factor. This association leads to Act1-mediated K63-linked ubiquitination of SF2/ASF, resulting in its dissociation from mRNA and enabling stabilization of relevant transcript [67]. Moreover, Act1 also polyubiquitinates the second additional regulatory protein, HuR. While polyubiquitination of SF2/ASF leads to its disassociation from mRNA, polyubiquitinated HuR is able to bind and stabilize chemokine CXCL1 mRNA and also conduce its translation. In addition, deletion in HuR leads to rapid mRNAs decay [68]. In summary, HuR protein regulates mRNA either post-transcriptionally or translationally. Altogether, polyubiquitination of either destabilizing SF2/ASF factor or HuR protein enables stabilization of mRNA of proinflammatory cytokines, although the result of polyubiquitination of both components is inverse. Due to this, Act1 may form two different complexes, comprised either of Act1-TRAF2/5-SF2/ASF or Act1-TRAF2/5-HuR, both contributing to mRNA stabilization [68].

In summary, IL-17A/F, as a member of proinflammatory cytokine family, is capable of inducing the mRNA stabilization of cytokines contributing to inflammatory immune responses. Although TNFα-induced CXCL1 mRNA was found to be a primary target transcript for IL-17A/F, many other mRNAs, such as CXCL2 (MIP-2) or CCL2 (MCP-1) have prolonged half-life upon its stimulation. This suggests mRNA stabilization as a principal mechanism by which IL-17A/F induces gene expression [66]. By contrast, mRNA instability is a crucial mechanism of regulation of proinflammatory genes expression, thus controlling the extent of immune responses.

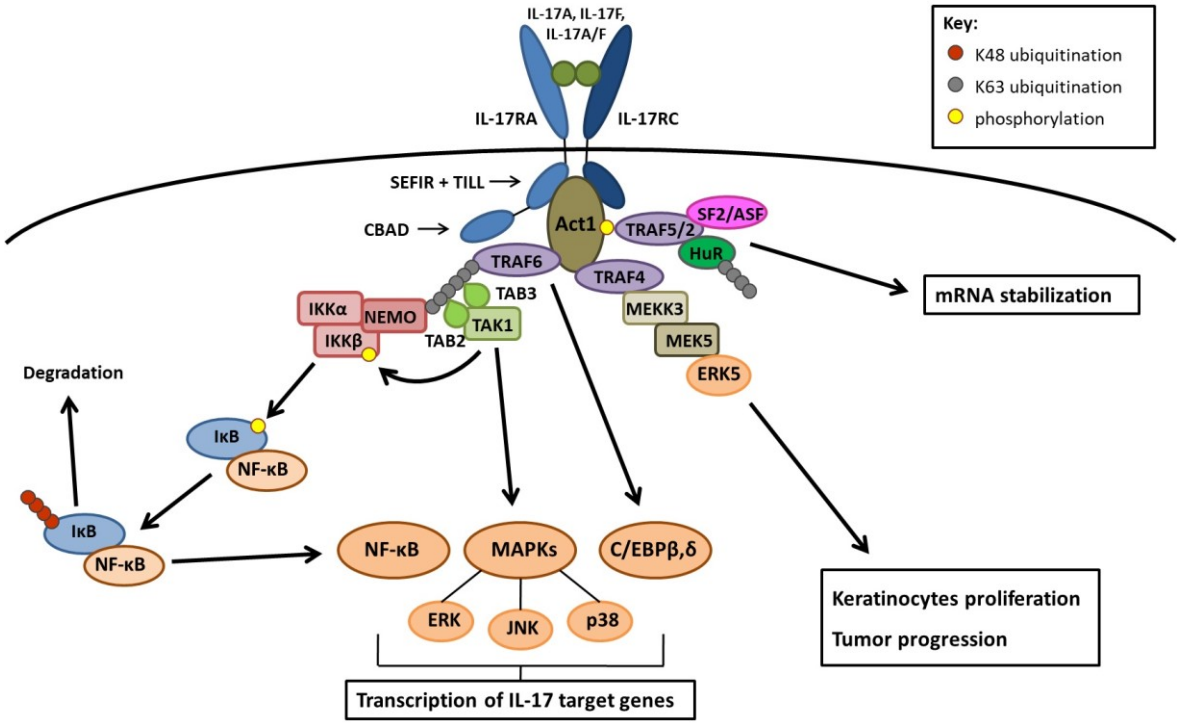

Figure 2. IL-17A/F-mediated signaling and activation of several downstream pathways: *Upon binding of either IL-17A, IL-17F homodimers or IL-17A/F heterodimer, their receptor composed of IL-17RA and IL-17RC subunits is able to recruit Act1 via SEFIR domains present in both IL-17RA/RC and Act1. Afterwards, Act1 initiates several downstream pathways through binding of different TRAF proteins. TRAF6-triggered gene activatory signaling pathways NF-κB, MAPKs or C/EBPs lead to transcription of IL-17A/F target genes, especially proinflammatory cytokines and chemokines, whereas TRAF5/2 and associated proteins contribute to stabilization of nascent mRNA transcripts. Moreover, additional pathway leading to activation of another MAP kinase, ERK5, and resulting in cell proliferation was found after binding of TRAF4.*

4. Regulation of IL-17A/F signal transduction

IL-17A/F act as a crucial cytokines contributing to initiation of inflammatory responses via their ability to activate several signal pathways (described above). Due to this, regulation of these pathways has a special importance in order to prevent chronic inflammation and autoimmune disorders. In general, a variety of activators and inhibitors has been linked to IL-17A/F-mediated signaling. Activators of IL-17A/F signal transduction represent mainly components enabling this signal pathway, such as Act1, TRAF6 etc. Thus, this section primarily focuses on delineation of negative regulators of IL-17A/F pathways (summarized in Figure 3.).

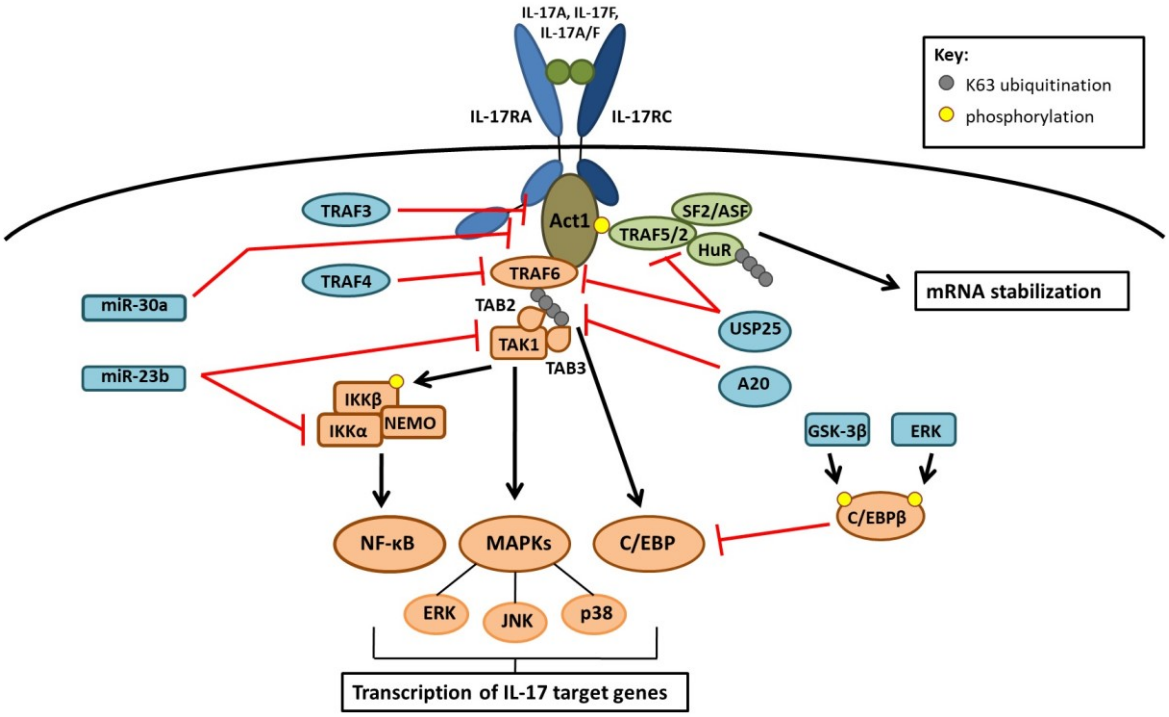

Figure 3. Negative regulation of IL-17A/F signaling: *IL-17A/F signaling pathways are regulated by various inhibitors, including kinases (ERK, GSK-3β), ubiquitinases (TRAF3, TRAF4), deubiquitinases (A20, USP25) or micro RNAs (miR-30a, miR-23b). This negative regulation is mediated by several mechanism and targets different molecules of IL-17A/F signal cascades.*

4.1. TRAF family proteins regulates IL-17A/F signaling

TRAF family consists of six members, TRAF1 to TRAF6 and majority of these proteins are involved in regulation of IL-17A/F signaling. Individual members of TRAF family can act both as activators and inhibitors of IL-17A/F-mediated signal pathways. As described above, TRAF6 is a key mediator of IL-17A/F-mediated NF-κB and MAPKs pathways, while TRAF2 or TRAF5 are related to IL-17A/F-induced mRNA stabilization. These observations suggest that diverse proteins of this family dictate distinct downstream signaling pathways [71]. Additionally, two other TRAFs were connected to inhibition of IL-17A/F signaling, especially TRAF3 and TRAF4 (Figure 3.).

TRAF3 binds to distal domain of IL-17RA/RC heterodimer via its TRAF domain [72]. This binding disrupts the formation of IL-17RA/RC-Act1-TRAF6 complex and represses initiation of signal pathways such as NF-κB and MAPKs.

TRAF4 is another inhibitor linked to suppression of IL-17A/F signaling and its knockout results in increased expression of chemokines such as CXCL1 upon IL-17A/F stimulation. Interaction of TRAF4 with Act1 prevents binding of TRAF6 and hence suppresses expression of proinflammatory cytokines [73]. Thus, TRAF3 and TRAF4 may reduce the development of autoimmune diseases such as EAE, whereas their ablation promotes IL-17A/F signaling leading to inflammation process [72, 73].

Apart from inhibitory role of TRAF4 in IL-17A/F-mediated proinflammatory cascades, it was linked to another additional pathway, which promotes stimulation of keratinocytes proliferation and tumor progression. After interaction with Act1 TRAF4 forms a complex with MEKK3 and MEK5, which afterwards recruits and activates MAP kinase ERK5 (Figure 2.). However, TRAF4 failed to activate other MAPKs in IL-17A/F signaling, such as JNK and p38, suggesting that TRAF4 acts differently on various MAPKs [74].

4.2. Deubiquitination negatively affects IL-17-mediated signaling

Nondegradative ubiquitination plays a crucial mechanism that promotes IL-17A/F signal transduction. Thus, deubiquitination serves as a regulatory process controlling expression of proinflammatory cytokines and inflammation development. Deubiquitinases (DUBs) are enzymes that cleave attached ubiquitin molecules from target proteins and several DUBs are involved in IL-17A/F signaling regulation (Figure 3.).

A20 is an important DUB which acts as a negative regulator in variety of signaling pathways [75]. In the case of IL-17A/F stimulation, A20 inhibits NF-κB pathway, as it cleaves K63 ubiquitin chains attached to TRAF6. However, it is not required for IL-17A/F-mediated mRNA stabilization. A20 is encoded by *TNFAIP3* gene, and its expression increases upon IL-17A/F stimulation in NF-κB dependent manner. A20 interacts directly with IL-17RA, especially with its distal inhibitory CBAD domain. In conclusion, A20 forms a negative feedback loop inhibition of IL-17A/F signaling as it restricts initiation of NF-κB and MAPKs pathways, thus controlling production of inflammatory cytokines [76, 77].

Another deubiquitinase influencing IL-17A/F signalization is ubiquitin-specific protease 25 (USP25) which associates with either TRAF5 or TRAF6. Due to this, overexpression of USP25 suppresses IL-17A/F-induced activation of several signal pathways as well as IL-17A/F-induced mRNA stabilization. By contrast, its defects promote increased phosphorylation of MAPKs or IKK complex which may lead to the development of chronic inflammation or autoimmune disorders [78].

4.3. Kinases IKKi and TBK1 regulates IL-17A/F signal pathways

IκB kinase-ε (IKKε, also called IKKi) and TANK-binding kinase-1 (TBK1, also known as NF-κB-activating kinase (NAK)) are two homologues kinases that are also highly similar to IKKα and IKKβ. They were originally considered to enhance expression of inflammatory cytokines via NF-κB pathway [79], but subsequent studies demonstrated that both TBK1 and IKKε are not promoting NF-κB activation. Instead, IKKε was found to be involved in MAPKs pathways activation [80]. Upon IL-17A/F stimulation, IKKε forms complex with Act1, a crucial protein in IL-17A/F signaling and mediates its phosphorylation on serine 311. This phosphorylation activates pathway leading to IL-17A/F-induced mRNA stabilization. IKKε-phosphorylated Act1 recruits TRAF2 and TRAF5, together forming a complex, which enhances the stability of nascent mRNA transcripts (described above) [80]. In addition, phosphorylation of Act1 on Ser311 inhibits binding of TRAF6, as this serine is located nearby TRAF-binding domain. Thus, IKKε prevents Act1-TRAF6-induced activation of NF-κB. This observation suggests that IKKε is a crucial factor that controls interaction of Act1 with diverse TRAFs. Thus, IKKε is considered as a vital component in IL-17A/F-mediated signaling, primarily able to bifurcate different IL-17A/F signal pathways such as MAPKs signaling and chemokine mRNA stabilization (Figure 4.).

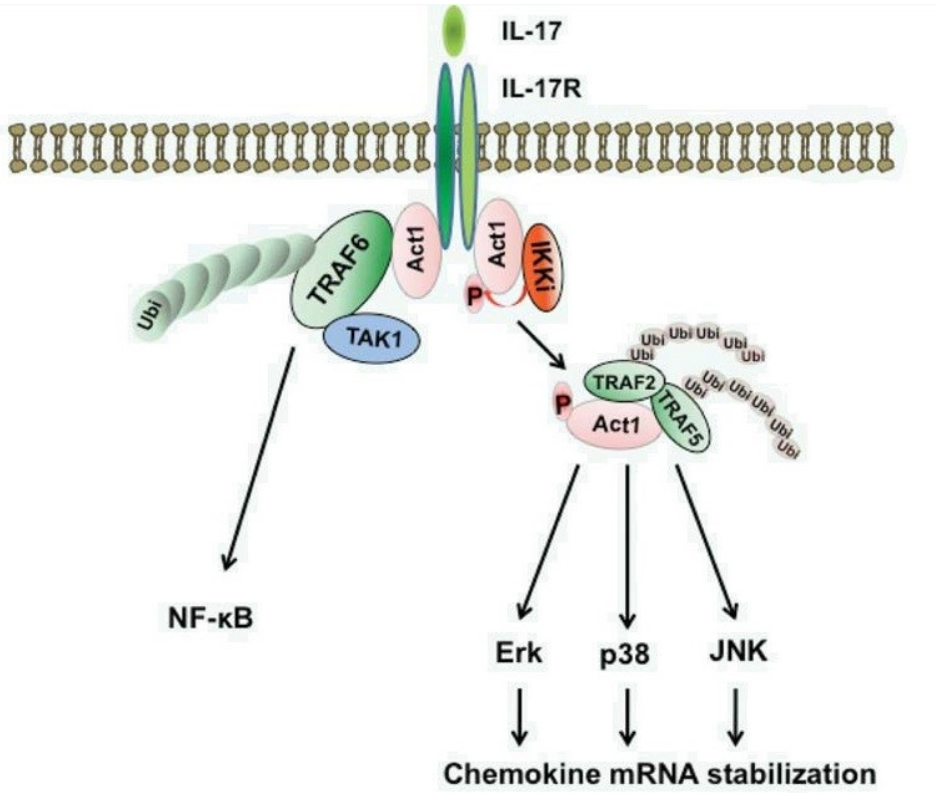

Figure 4. IKKε and its impact on IL-17A/F signaling: *After binding of IL-17A/F to its receptor Act1 binds and ubiquitinates TRAF6, leading to recruitment of other signal components and resulting in activation of NF-κB pathway. By contrast, Act1 is phosphorylated in the presence of IKKε, thereby forming a different complex with TRAF2 and TRAF5, which promotes activation of other pathways leading to stabilization of mRNA transcripts. Adapted from [81].*

Additionally, TBK1 also contributes to stabilization of IL-17A/F-induced mRNAs by suppression of decapping of mRNA transcripts [82]. In summary, both kinases IKKε and TBK1 act as a key mediators in expression of proinflammatory cytokines.

4.4. MicroRNAs-mediated regulation

MicroRNAs (miRNAs) show an appreciable importance in regulation and modulation of immune responses. Expression of most miRNAs is regulated by activated NF-κB pathway and some of them were shown to be implicated as suppressors in regulation of IL-17A/F signal transduction. In fact, IL-17A/F-induced NF-κB activation downregulates expression of miR-23b and miR-30a [83, 84]. In addition, IκB-ζ factor, which is strongly upregulated upon IL-17A/F stimulation, was established as another regulator contributing to miR-23b

expression as it binds to miR-23b promotor and contributes to higher expression of miR-23b [83]. Thus, these data suggest possible formation of negative feedback loop.

The miR-23b primarily targets mRNA for TAB2/TAB3 or IKK-α, a key components of IL-17A/F signal pathways, which results in reduced production of inflammatory cytokines [83]. The second miRNA involved in IL-17A/F signaling regulation, miR-30a, directly targets mRNA for Act1, thus either causing its degradation or preventing its translation. This results in both disrupted activation of NF-κB and MAPKs pathways and prevention of chemokine mRNAs stability [84]. Thus, miR-30a inhibits both TRAF6-dependent and independent downstream pathways. Moreover, titers of both miR-30a and miR-23b were significantly reduced in patients suffering from autoimmune disorders such as rheumatoid arthritis, indicating their probable suppressive role in autoimmunity [83, 84]. In summary, miRNAs involved in IL-17A/F-mediated signal transduction act as important suppressors contributing to decreased production of inflammatory cytokines (Figure 3.).

5. Mutations affecting IL-17A/F signal transduction

As mentioned earlier, IL-17A/F-induced signaling pathways result mainly in the production of cytokines, which contribute to and maintain IL-17A-initiated proinflammatory immune responses. Several deficiencies were described within IL-17A signal pathways, leading to attenuated inflammatory responses and insufficient host defense. These defects primarily include autosomal recessive (AR) deficiencies in IL-17RA or IL-17RC receptor subunits, AR Act1 deficiency and also decreased production of IL-17A/IL-17F cytokines themselves. Defects in both IL-17R receptor subunits are complete, while defects in their cytokines are only partial (described for IL-17F) [85, 86]. In conclusion, patients with any of these mutations suffer from many infections caused by invading pathogens, especially chronic mucocutaneous candidiasis disease (CMCD), as they are unable to respond to IL-17A/F stimulation. Except for CMCD, patients with either IL-17RA or Act1 deficiency also suffer from staphylococcal skin infections or respiratory infections cause by various bacteria [87, 88]. Also, patients with deficiency in both receptor subunits IL-17RA and IL-17RC are highly susceptible to oropharyngeal candidiasis [86].

In general, IL-17RA, as a common receptor subunit for IL-17 family, is required for IL-17A/F-mediated signaling. Binding of IL-17A/F to its receptor initiates processes leading to inflammatory responses. These processes include for example cytokine production at epithelial surfaces or infiltration of various cells including eosinophils, neutrophils and Th2 cells. Due to this, IL-17RA deficiency results in skin inflammation, microbial dysbiosis at mucosal surfaces and loss of skin and mucosal barrier as a consequence of dysregulation of IL-17A/IL-17RA axis [88].

Patients with defect in IL-17RC also evince the increase tendency to CMC. All tested patients were a homozygotes with several distinct non-sense mutations in alleles encoding IL-17RC, thus impeding expression of IL-17RC at cell surfaces [85]. Deficiency in entirely IL-17RC subunit abolishes signal pathway of IL-17A and IL-17F, but has no impact on other IL-17 ligands, as this subunit doesn't serve as their receptor [85], in contrast to IL-17RA, which serves as a receptor subunit for majority of IL-17 ligands.

In case of Act1, a biallelic missense mutation (T536I) was described, located in its SEFIR domain. This mutation disables binding of Act1 to IL-17RA/RC or other subunits, leading to ablation of IL-17A/F signaling [89]. In summary, patients unable to respond to IL-17A/F suffer from CMC diseases. These observation prove that proper activation of IL-

17A/F-mediated signaling pathway has a pivotal role in host defense against various extracellular pathogens and infections.

6. Other IL-17 family members

Except for functionally and structurally related IL-17A and IL-17F, there are 4 additional members that also belong to interleukin-17 family. However, they may form a separate subclass of the family according to their structural and sequential difference from IL-17A. This section focuses on the description and characterization of other IL-17 family members.

6.1. IL-17B and IL-17C as other proinflammatory family members

Both IL-17B and IL-17C share amino acid sequence homology with IL-17A and are one of the most distinct members of the family. Moreover, IL-17B is secreted as a non-covalent dimer [23]. IL-17B and IL-17C are expressed in various human tissues. The first IL-17B and its mRNA transcript were found to be expressed mostly in adult pancreas, small intestine and stomach, but no expression was found in activated $CD4^+$ T cells. Structure of its receptor is still not completely discovered, however, it consists of at least one IL-17RB [3].

IL-17C is expressed mainly by infected epithelial cells [90] and binds to heteromeric IL-17RA/IL-17RE receptor complex. Whereas IL-17RA could be found on the surfaces of various cell types, IL-17RE receptor subunit is highly expressed in Th17. Thus, after binding to this complex IL-17C is able to regulate differentiation and development of Th17 cells and autoimmune diseases [91]. In contrast to IL-17A/F, either IL-17B or IL17C can stimulate a human leukemic monocytic cell line (THP-1) to increased production of TNF-α and IL-1β, whereas IL-17A/F induce only a low levels [90]. These observations suggest that both IL-17B and IL-17C may have an important function in inflammatory responses [91].

6.2. IL-17D and its biological activity remains poorly understood

IL-17D is the least understood cytokine of family and also its receptor remains unknown. It was identified as a tumor-expressed cytokine, primarily secreted in highly immunogenic tumors. Its biological activity consists in inducing tumor endothelial cells to produce chemokine CCL2, leading to the recruitment of natural killer cells (NK) and their infiltration into tumor microenvironment [92]. Subsequently, NK cells activate development of M1 macrophages and then immune responses [93]. Thus, IL-17D plays important role in

suppression of tumor progression. However, IL-17D-mediated tumor rejection is achieved mainly indirectly by initiating antitumor activity and immunity, instead of destruction of tumor cells [92].

6.3. IL-17E as a member with distinct biological activity

IL-17E, also known as IL-25, is probably the most distinct member of IL-17 family. It has only 20% amino acid similarity with IL-17A. Unlike the other members, it's considered to be involved in Th2 mediated immune responses [94]. It binds to heteromeric receptor consisting of IL-17RA and IL-17RB. IL-17RB subunit is shared with another family member IL-17B and is highly expressed in the kidney, liver and Th2 cells. Its overexpression induces differentiation and cytokine production in Th2 cells as well as mucus production in epithelial cells. Main cytokines produced upon IL-25 stimulation include IL-4, IL-5 and IL-13 and together with mucus provide host against parasitic infections, caused for example by *Trichuris muris* [95, 96]. However, overexpression of IL-25 also induces IgE expression which could result in allergic pathologies. Thus, IL-25 appears as a crucial factor in regulating the initiation of pro-allergic responses [95].

IL-25-induced production of IL-13 has a pivotal role in inhibition of several cytokines, such as IL-23, IL-6 or IL-1β, which results in suppression of Th17 responses and potential development of autoimmune disorders. Thus, blockade of IL-25 leads to development of experimental autoimmune encephalomyelitis (EAE), an autoimmune inflammatory disease of central nervous system (CNS). In addition, IL-25 is highly expressed in CNS and resident microglia were found to be a primary source of this cytokine. During the CNS inflammation, there are manifoldly higher titers of IL-25 produced by microglia [94]. In general, IL-25 is highly expressed in that tissues, where inflammation needs to be regulated. These tissues include for example digestive and respiratory tracts or immunologically privileged sites. Development of inflammation in these tissues may led to the destruction of commensal microbes or the tissue itself. These findings suggest that the roles of IL-25 and IL-17A, although being members of the same family, are opposite in the pathogenesis of autoimmunity [94].

7. Conclusion

IL-17A and IL-17F and their receptor IL-17RA/RC have a crucial role in host protection against infections caused by invading pathogens. Although IL-17A/F act only as modest mediators of gene-activatory signaling, their ability to synergize with other cytokines and stimuli amplifies their biological activity. This text summarized existing data about IL-17A/F function and molecular mechanisms mediating their signaling, which may provide important information about their role in chronic inflammation.

IL-17A/F induce production of a variety of proinflammatory cytokines via initiation of several signal cascades, including NF-κB and MAPKs, or via stabilization of nascent mRNA transcripts. These pathways are necessary to activate during initiation of infection, while strict regulation is needed to protect host tissues against damage caused by chronic inflammation and development of autoimmunity. Especially, IL-17A/F contribute to the formation of psoriatic plaques and development of rheumatoid arthritis, EAE or lupus erythematosus. Currently, several biological agents, such as suppressors and monoclonal antibodies are in clinical use to treat moderate-to-severe plaque psoriasis, but are less thriving in treatment of rheumatoid arthritis. These monoclonal antibodies include those targeting IL-17A/F cytokines, IL-17R or IL-23 cytokine crucial for maturation of Th17 cells and subsequent production of IL-17. Although this antibody therapy shows as promising and effective way in treatment of psoriasis, it is still extremely expensive, with many observed side effects in treated patients, which might be eliminated only after long-term trials with a high number of tested patients, thus determining this therapy highly demanding.

Due to this, the question remains whether there are another possible target molecules within IL-17A/F-mediated signaling pathways which may be targeted for treatment of several autoimmune disorders. Study of IL-17-induced signaling may reveal new approaches to alleviate autoimmune disorders in patients suffering from autoimmunity and chronic inflammation via improvement of existing therapies.

8. References

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